Remarks

Amendments to the Claims

Claim 11 has been amended to correct its dependency so that it depends from claim 38. No new matter has been added by way of this amendment, entry of which is respectfully requested. Applicants believe that it is proper for the present amendment to be entered since it places the claims in better form for appeal, does not raise any new issues, and does not require further consideration or search.

In the Advisory Action mailed September 5, 2007, the Examiner indicated that the Amendment and Response filed August 20, 2007 overcame the previous rejection of claims 28-33 under 35 U.S.C. § 112, second paragraph.

The remaining comments are identical to the arguments previously presented in the Amendment and Response filed August 20, 2007.

Rejection Under 35 U.S.C. § 102

Claims 1, 3-6, 8-18, 20-24, 26, 28, 33-36, and 38 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 6,071,497 to Steiner, *et al.* ("the '497 patent") and claims 1, 4-10, and 13-36 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,652,885 to Steiner, *et al.* ("the '885 patent"). The Office Action refers to U.S. Patent No. 6,107,497 in this rejection; however this appears to be a typographical error. Therefore Applicants have assumed that the Examiner intended to refer to U.S. Patent No. 6,071,497 to Steiner, *et al.* Applicants respectfully traverse this rejection.

The '497 patent

The '497 patent describes a drug delivery system comprising a complex of diketopiperazine and drug to be delivered. The '497 patent discloses administration of the drug to the pulmonary system (*see e.g.* abstract). In Example 1, the '497 patent discloses a study of the administration of salmon calcitonin (sCT)-diketopiperazine microparticles to sheep. Following instillation of the microparticles in each lung of the sheep, the blood was sampled, collected, and analyzed to determine that blood plasma concentrations of sCT. These results were compared to the blood plasma concentrations of sCT obtained following subcutaneous injection of sCT. The results showed rapid absorption of sCT into blood plasma following administration to the lung and via subcutaneous injection (col. 11, lines 62-64).

However, a discussion of blood plasma levels does not disclose or suggest administration of a compound through a cell membrane and directly into the cell. For example, drug transfer from the lung to the blood in the cephalic vein, may occur via transport between cells. As discussed in, Patton, et al., "*The Lungs as a Portal of Entry for Systemic Drug Delivery*", Proc. Amer. Thorac. Soc., 1:338-344 (2004) ("Patton") (a copy of which was submitted with the Amendment and Response filed January 5, 2007), the "precise mechanisms of macromolecule absorption in the lungs are not well known." (*Id.*, page 341, right col., first full para.) Patton indicates that generally "exogenous macromolecules are thought to be absorbed from the airspaces nonspecifically". (*Id.*) Thus, the mere disclosure in the '497 patent regarding the blood serum levels of calcitonin does not disclose or suggest administration into a cell, let alone that a

complex containing the compound to be delivered and DKP can enhance transport through a cell membrane containing a lipid bilayer. Therefore, claims 1, 3-6, 8-18, 20-24, 26, 28, 33-36, and 38 are not anticipated by the '497 patent.

The '885 patent

The '885 patent describes a method for purifying peptides and proteins by incorporating them into diketopiperazines to facilitate removal of one or more impurities. Like the '497 patent discussed above, the '885 patent discloses blood levels of drug, such as insulin, following administration, such as via inhalation, and compares these levels with the levels achieved following subcutaneous injection with the drug. (*see e.g.* col. 10, line 62 until col. 11, line 3, comparing blood levels of insulin following pulmonary administration of insulin in fumaryl diketopiperazine with blood levels of insulin following subcutaneous injection).

However, a discussion of blood plasma levels does not disclose or suggest administration of a compound through a cell membrane and directly into the cell. For example, drug transfer from the lung to the blood in the cephalic vein, may occur via transport between cells. (*see e.g.* Patton) The '497 patent does not disclose or suggest administration into a cell, let alone that a complex containing the compound to be delivered and DKP can enhance transport through a cell membrane containing a lipid bilayer. Therefore, claims 1, 4-10, and 13-36 are not anticipated by the '885 patent.

Rejection Under 35 U.S.C. § 103

Claims 1, 3-36 and 38 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the '497 patent, in view of the '885 patent. Applicants respectfully traverse this rejection.

Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459 (1966). The *Graham* analysis was recently affirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

The Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). This analysis is commonly referred to as the "TSM test". Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

> The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of

> ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. [. . .] There is no necessary inconsistency between the [TSM] test and the *Graham* analysis.

KSR, 127 S. Ct. at 1727.

The obviousness analysis requires looking at the invention as a whole. "Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986).

Hindsight analysis, such as picking and choosing from prior art references using the claimed invention as a template, has long been forbidden. *See e.g. In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988), stating "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." In *KSR*, the Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (*KSR*, 127 S. Ct. at 1742, citing *Graham*, 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use

of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6th Cir. 1964))).

In response to the *KSR* decision, the Deputy Commissioner for the USPTO issued a memorandum stating: "[I]n formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Memorandum from Margaret A. Forcarino to Technology Center Directors (May 3, 2007).

Analysis

The cited references do not recite each and every element of the claims

As discussed above, neither the '497 patent nor the '885 patent disclose or suggest a method for enhancing transport of a compound across a cell membrane comprising a lipid bilayer, much less how to administer a drug directly to a cell. Therefore, since neither of the references alone discloses at least these elements of the claimed methods, the combination of the '497 patent with the '885 patent does not disclose all of the elements of the claimed methods.

The cited references do not provide one of skill in the art with a reasonable expectation of success

As discussed above, neither the '497 patent nor the '885 patent disclose or suggest delivery of a compound through a cell membrane directly to a cell. The '497 and the '885 patents focus on drug transport through an organ membrane, such as the lung, into the blood stream. The fact that transport of the drug occurred from the lungs into the blood stream does

not explicitly or inherently amount to a disclosure of transport into a cell through the cell's membrane. As described in Patton, transport into the blood stream occurs through different paths, including transport between cells. Therefore, one of ordinary skill in the art is not provided with a reasonable expectation of success based on the disclosures in the '497 patent and the '885 patent that a complex of compound and DKP can result in enhanced transport of the compound across a cell membrane and into the cell. Therefore, claims 1, 3-36 and 38 are not obvious over the '497 and '885 patents.

Allowance of claims 1, 3-36 and 38, as amended, is respectfully solicited.

Respectfully submitted,

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